Materials and Methods: *In vitro*, we examined the effect of AT-101 (kindly provided by Ascenta Therapeutics Inc.) radiation and the combination on apoptosis induction and clonogenic survival in two HNSCC cell lines that expressed the target proteins: UM-SCC-11B (derived from a primary tumor of the larynx) and VU-SCC-OE (derived from a primary tumor of the oral cavity). Apoptosis was determined by *bis*-benzimide staining to detect morphological nuclear changes and/or by propidium iodide staining and flow-cytometry analysis to quantify sub-diploid apoptotic nuclei. The type of interaction between AT-101 and radiation was evaluated by determining the Combination Index (CI) and isobolographic analysis. In addition, we assessed clonogenic survival upon combined treatment in the VU-SCC-OE cell line. In the clinical study, N07CRH, patients with locally advanced HNSCC, were enrolled in a two-arm trial design with standard radiotherapy/cisplatin treatment combined with concurrent dose-escalating oral AT-101 according to two different schedules, a 2-weeks daily schedule every 3 weeks, and a pulse-dose schedule on 3 consecutive days, every 3 weeks. Blood samples were collected and serum concentrations of AT-101 were determined by HPLC methods.
Results: *In vitro* results showed that AT-101 (10-15 μM) enhances radiation(5Gy)-induced apoptosis with CI's ranging from 1.1 (additive) to 0.74 (synergistic). Clonogenic survival assays showed a radiosensitizing effect with a DEF_{37} of 1.3 at concentrations of AT-101 that were markedly lower than used for apoptosis studies. Patients tolerated AT-101 well up to doses of 20 mg. Pharmacokinetic analyses of blood samples taken from the patients at time intervals from 30 minutes up to 24 hours after oral intake showed a dose-dependent increase in serum concentration with peak concentrations up to 300 - 700 ng/ml (0.5 – 1.2 μM) between 2 and 2.5 hours after intake.
Conclusions: AT-101 is a competent enhancer of radiation-induced apoptosis in HNSCC *in vitro*. In addition, *in vitro* radiosensitization was observed at clinically achievable serum levels. These finding support further evaluation of the combination of AT-01 with radiation in Bcl-2-overexpressing tumors.

PO-1061

Radiosensitisation properties of PI3K/AKT inhibitor GDC-0941 in prostate cancer cells

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Purpose/Objective: Radiation therapy is a primary treatment modality for prostate cancer. Over activation of the phosphoinositide 3-kinase (PI3K) pathway causes radioresistance increasing cell survival following radiation, resulting in treatment failure and disease recurrence. Downstream effects of PI3K increase HIF1-α concentrations resulting in high levels of hypoxia in PI3K activated prostate cancer cells. This study investigated the effect of PI3K inhibitor, GDC-0941, on the radiosensitisation of cell lines DU145 and 22Rv1 under hypoxic and normoxic conditions.
Materials and Methods: GDC-0941 was combined with radiation treatment to assess the radiosensitisation effect in DU145 and 22Rv1 cell lines. GDC-0941 was also tested under hypoxic conditions to assess if radiosensitivity was maintained. Clonogenic assays were used to assess cell survival under the varied treatment conditions.
Results: GDC-0941 was shown to enhance radiosensitivity in both 22Rv1 (2Gy: SER=1.7, p=0.038) and DU145 (2Gy: SER=2, p=0.0025). The radiosensitisation conferred was also significant under hypoxic conditions in 22Rv1 (2Gy: SER=2, p=0.0155) although non-significant in DU145 (2Gy: SER=1.1, p=0.1835). GDC-0941 showed comparable radiosensitisation under both normoxic and hypoxic conditions in both cell lines.
Conclusions: GDC-0941 radiosensitised prostate cancer cells under hypoxic and normoxic conditions.

PO-1062

Radiosensitization of tumor cells by Paclitaxel relies on chromosome missegregation and depends on TPX2

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Purpose/Objective: The anti-neoplastic compound Paclitaxel (Taxol®) is adopted for multiple strategies of cancer treatment encompassing classic chemotherapy on the one side as well as adjuvant treatment settings that combine chemotherapy with other treatment modalities like radiation therapy on the other. The molecular mechanism(s) by which Paclitaxel exerts radiosensitization of tumor cells is not understood in full detail. Moreover, the doses of Paclitaxel that are currently applied in the clinic often coincide with side effects of major severity. Finally, no stratification markers that allow for predicting the responsiveness of tumors towards treatment schedules involving Paclitaxel and radiotherapy are available thus far.
Materials and Methods: Multiple concentrations of Paclitaxel were screened for respective effects on the viability and the proliferation of tumor cells. After identifying low nanomolar doses of Paclitaxel to impact tumor cell proliferation and -viability in a hitherto highly neglected manner, a cohort of tumor cell lines was screened for individual differences in susceptibility towards equivalent doses of Paclitaxel, either administered alone or in combination with irradiation. Based on this screen, a search for new stratification markers was performed.
Results: We show that Paclitaxel at lower nanomolar concentrations effectively sensitizes tumor cells towards ionizing radiation by facilitating high-grade aneuploidization. At such concentrations, Paclitaxel renders the ordinary, bipartite mode of cell division into a highly non-equational, mainly tripartite one thereby facilitating huge levels of aneuploidization and this is frequently followed by a distinct kind of apoptotic cell death. We show that this effect can be correlated with Paclitaxel-dependent radiosensitization of tumor cells since cell lines that are resistant to it are sensitized to lesser extends. We also provide evidence that both, Paclitaxel-dependent aneuploidization and -radiosensitization of tumor cells correlate with the expression levels of AURKA and TPX2, two proteins involved in mitotic spindle assembly, since a knockdown of TPX2 not only rescues the bipartite mode of cell division in the presence of Paclitaxel but also diminishes the radiosensitization effect that is achieved by Paclitaxel.